# PATENT ABSTRACTS OF JAPAN

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## (54) STABLE PERNASAL PREPARATION OF BUPRENORPHINE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a pernasal preparation of buprenorphine capable of rapidly removing pain of patients and simply administering and being physically stable.

SOLUTION: This powdery pernasal preparation comprises buprenorphine, a slightly water-soluble and water-absorbable base, a water-soluble and gel- forming base and stearic acid. It is preferable that the slightly water-soluble and water-absorbable base is one or two compounds selected from a group comprising crystalline cellulose, α-cellulose, crosslinked dextrin, chitin and chitosan and the water-absorbable and gel-forming base is a lower alkyl ether of cellulose.

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## CLAIMS

[Claim(s)]

[Claim 1] Buprenorphine, powdered pernasal pharmaceutical preparation which is water poor solubility, is the basis of water absorptivity, and water absorptivity, and consists of a basis of a gel plasticity, and stearin acid.

[Claim 2] Powdered pernasal pharmaceutical preparation according to claim 1 which is 1 chosen from the group which it is this water poor solubility, and the basis of water absorptivity becomes from crystalline cellulose, alpha cellulose, a bridge formation dextran, a chitin, and chitosan thru/or 2 or more.

[Claim 3] Powdered pernasal pharmaceutical preparation according to claim 1 or 2 whose basis of a gel plasticity it is this water absorptivity and is low-grade alkyl ether of a cellulose.

[Claim 4] Powdered pernasal pharmaceutical preparation given in any 1 term of claims 1-3 which are 1 chosen from the group which the low-grade alkyl ether of this cellulose becomes from hydroxypropylcellulose, hydroxypropyl ethyl cellulose, a carboxymethyl cellulose, carboxymethylcellulose sodium, and carboxymethyl-cellulose calcium thru/or 2 or more.

[Claim 5] Powdered pernasal pharmaceutical preparation given in any 1 term of claims 1-4 whose contents of this stearin acid are 0.1 - 10 % of the weight in pharmaceutical preparation.

[Claim 6] Powdered pernasal pharmaceutical preparation given in any 1 term of claims 1-4 whose contents of this stearin acid are 1 - 10 % of the weight in pharmaceutical preparation.

[Claim 7] Powdered pernasal pharmaceutical preparation given in any 1 term of claims 1-6 whose contents of this buprenorphine are 0.5 - 30 % of the weight in pharmaceutical preparation.

[Claim 8] this water poor solubility -- and the basis of water absorptivity and this water absorptivity -- and powdered pernasal pharmaceutical preparation given in any 1 term of claims 1-7 the range of whose mixing ratios of the basis of a gel plasticity is 99:1-70:30 in a weight ratio.

## DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the pernasal powder material of stable buprenorphine. In more detail, this inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and relate to the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid. the patient who has a pain according [ this invention ] to a cancer disease, an operation, etc. -- a medical practitioner, a male nurse, and a patient -- by him etc., the absorption from a nasal cavity for eliminating the pain promptly [ a medicine is prescribed for the patient simple, and ] is prompt, and the effectiveness is high, and pharmaceutical preparation is provided with the pernasal powder material of stable buprenorphine.
[0002]
[Description of the Prior Art] A cancer pain, a postoperative pain, etc. are intolerable very pain pains for a patient. To these pains, as a remedy, narcotics or non-narcotics nature opioid is mainly used, and the morphine which is narcotics is marketed as injections, suppositories, and an oral agent as dosage forms of such medicine, and the fentanyl citrate which is narcotics is marketed as injections and a tape, and the buprenorphine which is non-narcotics nature opioid further is marketed as injections and suppositories, and is obtaining effectiveness for desensitization, respectively.
[0003] Moreover, the pernasal liquids and solutions of buprenorphine are shown in Journal of Pharmaceutics and Pharamcology Vol.41 803-805 1989 as simple administration dosage forms. The absorption from the nose of a drug is prompt compared with suppositories, an oral agent, etc., and about the same immediate effect nature as injection administration can be expected, and it is known that the prescribing [ for the patient ]-a medicine method is comparatively simple also for a user or a non-user.
[0004] As mentioned above, as for the pharmaceutical preparation which uses buprenorphine as a chief remedy, Kamiichi of suppositories and the injections has already been carried out. Moreover, in a current in and outside the country one, a tape, the pharmaceutical preparation in the oral cavity, etc. are developing as other dosage forms. however, the patient who has pain -- when it stands on a position of him or a person looking after a patient, desire of a patient and a person looking after a patient is not necessarily completely filled by them. That is, although the patient is anxious for escaping pain promptly and a person looking after a patient wants to respond to the hope that it is simple and quickly, in suppositories, from the description on the route of administration, slight blood drug concentration until the desensitization effectiveness shows up has time amount to be attained, and a patient has to fight with a pain in the meantime. moreover -- suppositories are sanitary from the description on the route of administration -- it cannot say -- a patient -- for him and a person looking after a patient, it is the pharmaceutical preparation which is hard to use. Furthermore, although injections can be promptly attained into blood in medicine and quick desensitization is possible for them, so, it also has troubles, like it reaches to an extreme and only qualified persons, such as that it is invasion-like, a medical practitioner, and a nurse, can be medicated to be ****ed and.
[0005] Then, the medication from a nose can be considered as mentioned above as a

means to make the simple nature and the prompt desensitization effectiveness of administration discover. It is shown to above-mentioned Journal of Pharmaceuticsand Pharamcology Vol.41 803-805 1989 by by medicating healthy people with the pernasal liquids and solutions of buprenorphine that the effective blood drug concentration of a drug was accepted promptly. However, even if it makes it this pharmaceutical preparation, in order to make it the pharmaceutical preparation which can actually be equal to a patient's clinical use, it is important [ the physical stability of the chief remedy buprenorphine in pharmaceutical preparation is very a problem, and ] to conquer the problem of this stability.

[0006]

[Problem(s) to be Solved by the Invention] The purpose of this invention cancels a patient's pain promptly, and offering the pernasal powder pharmaceutical preparation of stable buprenorphine also physically has the administration simple.

[0007]

[Means for Solving the Problem] That is, this inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and offer the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid.

[0008]

[Embodiment of the Invention] This inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and are the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid.

[0009] The buprenorphine of this invention is the partialness agonist of morphine, and it is known that the analgesic action is dozens times the morphine. That is, when buprenorphine controls the nociception conduction system of a central nervous system, sad effectiveness is demonstrated and chemical stimulation, thermal stimulation, pressure stimulation, and electrical stimulation are made into a noxious stimulus, it is known that an analgesic effect strong and longer than morphine and pentazocine is shown. Kamiichi of injections and the suppositories is carried out as current and buprenorphine hydrochloride. The buprenorphine of this invention has also included the buprenorphine which exists as a salt with the acid permitted pharmacologically, and is buprenorphine hydrochloride which is a hydrochloride preferably.

[0010] The basis (it may abbreviate to a "water poorly soluble basis" below) of the water poor solubility of this invention and water absorptivity is one sort chosen from crystalline cellulose, alpha cellulose, a bridge formation dextran, a chitin, and the group that consists of chitosan, or two sorts or more.

[0011] Also in these, as a water poorly soluble basis of this invention, one sort or two sorts or more of things chosen from the group which consists of crystalline cellulose, alpha cellulose, and chitosan are desirable, and can raise crystalline cellulose also especially with inside as a desirable thing.

[0012] It is the water absorptivity of this invention, and as for the basis (it may abbreviate to a "gel plasticity basis" below) of a gel plasticity, it is desirable that it is the low-grade alkyl of a cellulose, and it is desirable that they are one sort or two sorts or more of bases chosen from the group which consists of hydroxypropylcellulose, the hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose, and carboxymethylcellulose sodium especially. Hydroxypropylcellulose can be raised as a desirable thing even especially in inside.

[0013] Moreover, as for hydroxypropylcellulose, it is desirable that the viscosity of

the 2% water solution is 150-4,000cps. Viscosity here is kinematic viscosity and it is measured by viscometers, such as an object for canon-Fenske and canon-Fenske opaque liquid, Ubbelohde, and Ostwald. Measurement by the ubellohde's viscosimeter has a highly desirable precision especially. The bottom of a 37-degree C environment is asked for a viscosity value given in this specification by the ubellohde's viscosimeter by the Shibata science mechanical-engineering company. Although there is also a thing of hypoviscosity in hydroxypropylcellulose from this, when the thing of hypoviscosity is used rather than 150cps, the rise effectiveness of the maximum drug concentration of this invention is not sometimes necessarily enough.

[0014] As a desirable combination of the gel plasticity basis of this invention, and a water poorly soluble basis, each above suitable example comrade's combination is mentioned, and the hydroxypropylcellulose as a gel plasticity basis and the crystalline cellulose as a water poorly soluble basis can be especially mentioned as a desirable combination.

[0015] The mixing ratio of the gel plasticity basis and water poorly soluble basis which are used by this invention is a weight ratio, since pernasal absorption of a drug with the higher and early direction with few 1:99-35:65, and gel plasticity bases is attained, it is desirable, and it is desirable that it is 10:90-20:80 especially.

[0016] Although, as for the stearin acid of this invention, the use on pharmaceutical preparation is originally known as lubricant, as for the operating concentration in that case, 0.3 - 1% has been common sense for this contractor. Wholeheartedly, although stearin acid committed this invention persons also as lubricant as a result of examination so that it might be well-known, it found out stabilizing pharmaceutical preparation by adding more mostly than the amount of general [ used ]. This is clearer than the stabilization effect of this invention was accepted [ that functionality is in the addition and stability of stearin acid (refer to example), and ] neither with the magnesium stearate which are other lubricant, nor talc (refer to the example of contrast). Therefore, since it is desirable that it is 0.1 - 10% and the addition and stability of stearin acid have correlation as mentioned above about the content of the stearin acid of this invention, that it is more 1 - 5% especially leads to stabilization further, and it is more desirable than 0.5% used as lubricant.

[0017] Moreover, in the pernasal pharmaceutical preparation of this invention, since that it is 150 micrometers or less improves [ the effectiveness after administration ] the particle diameter of a drug deposition into a nasal cavity, it is desirable, and since higher and early pernasal absorption of a drug is attained, it is desirable to set mean particle diameter to 1-100 micrometers and further 1-20 micrometers by grinding, freeze drying, spray drying, etc. especially.

[0018] Moreover, in the pernasal pharmaceutical preparation of this invention, since higher and early pernasal absorption of a drug is attained, it is desirable that it is in the condition which a drug is unevenly distributed in a water poorly soluble basis, and is distributing rather than the gel plasticity basis. The following technique can be raised as the pharmaceutical preparation-technique of attaining this maldistribution.

1. Mix this water poorly soluble basis and a drug strongly mechanically. Subsequently, this gel plasticity basis is mechanically mixed weakly into this mixture.

2. Obtain the basis which the drug was made to adhere to this water poorly soluble basis by freeze drying or spray drying, and adhered the drug. Subsequently, it grinds and screening of the obtained basis is carried out so that the mean particle diameter of 90% of the weight or more of the particle may be set to 10-250 micrometers, and a powdered material is obtained. Then, this gel plasticity basis is mechanically mixed to

this powdered material.
3. Dissolve and distribute this water poorly soluble basis and a drug in organic solvents, such as ethanol, and mix this gel plasticity basis mechanically to this powdered material after carrying out the particle size regulation of the fine particles obtained by evaporating and making that organic solvent harden by drying to the mean particle diameter of 10-250 micrometers.
[0019] Since it is easy among the above-mentioned manufacture approaches to consider as the condition that a drug is unevenly distributed in a water poorly soluble basis, and is distributing rather than the gel plasticity basis in the 1st manufacture approach and the 2nd manufacture approach, it is desirable. For example, in case it mixes strongly in case a water poorly soluble basis is mixed with a drug by the 1st manufacture approach, and it subsequently mixes with a gel plasticity basis, it can mix weakly. In case the gel plasticity basis of the 2nd manufacture approach is mixed mechanically, it can mix strongly or weakly.
[0020] Here, manual forcing mixing by the others and the mortar which are a high speed mixer, a power full auto mixer, etc. which are the omnipotent mixer, the ribbon mixer, the automatic mortar, the ball mill, etc. and the other mixers whose mechanical mixing at the time of manufacturing the constituent of this invention is mixers of a container cover half, such as a V shaped rotary mixer which is a mixer of for example, a container rotation mold, a cross rotary mixer, and a duplex cone mold mixer, is also included.
[0021] Moreover, mixing by mixing by manual mixing according mixing strongly in the case of mixing to a mortar, the omnipotent mixer of a container cover half, a ribbon mixer, an automatic mortar, a ball mill, etc. and the high speed mixer, a powerful auto mixer, etc. is said, and homogeneity is mixed while a drug mainly adheres to a basis by this mixing. Moreover, mixing by the ball mill which does not use the V shaped rotary mixer of a container rotation mold, a cross rotary mixer, a duplex cone mold mixer, and a ball as mixing weakly is shown, and distributed mixing of the drug is mainly carried out independently of a basis at homogeneity.
[0022] Furthermore, the pernasal pharmaceutical preparation of this invention can be prepared also by specifying the particle diameter of a basis as follows besides the manufacturing method of the above 1-3, and since these invention objects can also attain early high pernasal absorption of a drug, they are desirable. As an approach of specifying the particle diameter of a basis, it is the range whose mean particle diameter of 90% of the weight or more of the particle of water poorly soluble ** this basis is 10 micrometers - 250 micrometers, and is the range whose mean particle diameter of the particle of 90 % of the weight or more of ** this gel plasticity bases is 10 micrometers - 105 micrometers, and the approach of preparing by making mean particle diameter of ** water poorly soluble basis larger than the mean particle diameter of this gel plasticity basis can be mentioned, for example.
[0023] Furthermore, when mean particle diameter of 90% of the weight or more of the particle of 10-250 micrometers and a gel plasticity basis is set to 10-65 micrometers for the mean particle diameter of 90% of the weight or more of the particle of a water poorly soluble basis, since the increment in the further maximum drug concentration can be acquired, it is desirable.
[0024] That it is in the range whose mean particle diameter of 90% of the weight or more of the particle of a basis is 10-250 micrometers here says what gave vibration with hand control or a machine, was specified by classifying powder, passed the sieve whose aperture of an eye is 250 micrometers using the trial sieve machine, and did not pass a 10-micrometer sieve. Under the present circumstances, while giving vibration,

it is a time of carrying out weighing capacity of the weight of the fine particles on each sieve, making the time of fluctuation of that weight becoming 0.1% or less into the terminal point of vibration, and the classification of fine particles being completed.

[0025] Moreover, even when the mean particle diameter of both bases is that the mean particle diameter of a water poorly soluble basis is larger than the mean particle diameter of a gel plasticity basis in above-mentioned numeric-value within the limits, respectively, it says that the numeric value of the mean particle diameter of a water poorly soluble basis is larger than the numeric value of the mean particle diameter of a gel plasticity basis.

[0026] Thus, the powdered pernasal administration constituent of this invention at the time of being prepared when the mean particle diameter of a water poorly soluble basis makes it larger than the mean particle diameter of a gel plasticity basis can be prepared according to the manufacturing method of common powdered pharmaceutical preparation for the person of this contractor of mixing mechanically a chief remedy, a water poorly soluble basis, and a gel plasticity basis.

[0027] By preparing according to the further above-mentioned manufacturing method of 1-3, since higher effectiveness can be acquired, it is desirable.

[0028] In addition, as the water poorly soluble basis and gel plasticity basis of this invention, unless it is contrary to the purpose of this invention, it has said specific property, and consists of a basis of a specific class, for example, it is desirable well-known as a basis which can be used for powder constituents for pernasal administration, such as starch and crystalline cellulose, to be able to use a microsphere and to use the thing of the range of 10 to 150 micrometers as a particle size of the particle in that case.

[0029] Moreover, to the constituent of this invention, the physical properties as pharmaceutical preparation, an appearance, or in order to improve that it is stinking etc., a well-known binder and a well-known diluent, a coloring agent, a preservative, antiseptics, an odor-masking agent, etc. may be added if needed. As a binder, if starch, a dextrin, etc. consider [ starch, a lactose etc. ] as; coloring agent as a; diluent, for example, and red No. 2 etc. considers [ an ascorbic acid etc. / p-hydroxybenzoic esters etc. ] as; odor-masking agent as; antiseptics as a; preservative, for example, menthol etc. is mentioned, for example.

[0030] Moreover, since the constituent of this invention is prescribed for the patient as pharmaceutical preparation, it is made into a suitable administration gestalt. As such a gestalt, there is a capsule filled up with this invention for every administration unit, and this is sprayed into a nasal cavity with a suitable administration vessel. moreover, the constituent of this invention of administration unit quantity or the constituent of this invention of the administration unit quantity for multiple times -- a suitable container -- containing -- the time of administration actuation -- the constituent of this invention of administration unit quantity -- single-dose administration -- or division administration may be carried out.

[0031]

[Effect of the Invention] Only injections or suppositories is conventionally marketed by this invention, but when a patient senses a pain for the buprenorphine which could not be prescribed for the patient only by the injection by the medical practitioner, or the rectum by the third person, the patient itself can prescribe a medicine now for the patient easily, desensitization can be performed promptly, and the effectiveness which this invention brings to a medical site can be called great thing.

[Example] An example explains this invention below.
[0033] [Examples 1-5] The pernasal pharmaceutical preparation which used buprenorphine as the chief remedy by the formula shown in the 1st following table was prepared.
[Table 1]

単位＝mg

| 実施例 | ブプレノルフィン | 結晶性セルロース | ヒドロキシプロピルセルロース | ステアリン酸 |
|---|---|---|---|---|
| 実施例1 | 40 | 1600 | 400 | 2 |
| 実施例2 | 40 | 1600 | 400 | 10 |
| 実施例3 | 40 | 1600 | 400 | 20 |
| 実施例4 | 40 | 1600 | 400 | 100 |
| 実施例5 | 40 | 1600 | 400 | 200 |

[0035] [Examples 1-3 of contrast] The pernasal pharmaceutical preparation which used buprenorphine as the chief remedy by the formula shown in the 2nd following table was prepared.
[0036] [Table 2]

単位＝mg

| 対照例 | ブプレノルフィン | 結晶性セルロース | ヒドロキシプロピルセルロース | 滑沢剤 |
|---|---|---|---|---|
| 対照例1 | 40 | 1600 | 400 | ステアリン酸マグネシウム：10 |
| 対照例2 | 40 | 1600 | 400 | タルク：10 |
| 対照例3 | 40 | 1600 | 400 | なし |

[0037] The result of having measured 20mg of contents under preservation by 60 degrees C and 40-degree-C75%RH at a time for the buprenorphine pernasal pharmaceutical preparation prepared by the buprenorphine pernasal pharmaceutical preparation prepared according to examples 1-5 and the examples 1-3 of contrast for the glass vial, respectively was shown in the 3rd table.
[0038] [Table 3]
ブプレノルフィン経鼻製剤の含量[%]変化

| 製剤 | 初期値 | 60℃保存4週間後 | 40℃75%RH保存6ヶ月後 |
|---|---|---|---|
| 実施例1 | 100 | 95.5% | 95.0% |
| 実施例2 | 100 | 95.0% | 96.0% |
| 実施例3 | 100 | 97.0% | 97.5% |
| 実施例4 | 100 | 99.0% | 99.0% |
| 実施例5 | 100 | 98.5% | 99.5% |
| 対照例1 | 100 | 75.0% | 64.0% |
| 対照例2 | 100 | 80.5% | 75.5% |
| 対照例3 | 100 | 80.5% | 80.0% |

## TECHNICAL FIELD

[Field of the Invention] This invention relates to the pernasal powder material of stable buprenorphine. In more detail, this inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and relate to the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid. the patient who has a pain according [ this invention ] to a cancer disease, an operation, etc. -- a medical practitioner, a male nurse, and a patient -- by him etc., the absorption from a nasal cavity for eliminating the pain promptly [ a medicine is prescribed for the patient simple, and ] is prompt, and the effectiveness is high, and pharmaceutical preparation is provided with the pernasal powder material of stable buprenorphine.

## PRIOR ART

[Description of the Prior Art] A cancer pain, a postoperative pain, etc. are intolerable very pain pains for a patient. To these pains, as a remedy, narcotics or non-narcotics nature opioid is mainly used, and the morphine which is narcotics is marketed as injections, suppositories, and an oral agent as dosage forms of such medicine, and the fentanyl citrate which is narcotics is marketed as injections and a tape, and the buprenorphine which is non-narcotics nature opioid further is marketed as injections and suppositories, and is obtaining effectiveness for desensitization, respectively.

[0003] Moreover, the pernasal liquids and solutions of buprenorphine are shown in Journal of Pharmaceutics and Pharamcology Vol.41 803-805 1989 as simple administration dosage forms. The absorption from the nose of a drug is prompt compared with suppositories, an oral agent, etc., and about the same immediate effect nature as injection administration can be expected, and it is known that the prescribing [ for the patient ]-a medicine method is comparatively simple also for a user or a non-user.

[0004] As mentioned above, as for the pharmaceutical preparation which uses buprenorphine as a chief remedy, Kamiichi of suppositories and the injections has already been carried out. Moreover, in a current in and outside the country one, a tape, the pharmaceutical preparation in the oral cavity, etc. are developing as other dosage forms. however, the patient who has pain -- when it stands on a position of him or a person looking after a patient, desire of a patient and a person looking after a patient is not necessarily completely filled by them. That is, although the patient is anxious for escaping pain promptly and a person looking after a patient wants to respond to the hope that it is simple and quickly, in suppositories, from the description on the route of administration, slight blood drug concentration until the desensitization effectiveness shows up has time amount to be attained, and a patient has to fight with a pain in the meantime. moreover -- suppositories are sanitary from the description on the route of administration -- it cannot say -- a patient -- for him and a person looking after a patient, it is the pharmaceutical preparation which is hard to use. Furthermore, although injections can be promptly attained into blood in medicine and quick desensitization is possible for them, so, it also has troubles, like it reaches to an extreme and only qualified persons, such as that it is invasion-like, a medical practitioner, and a nurse, can be medicated to be ****ed and.

[0005] Then, the medication from a nose can be considered as mentioned above as a

means to make the simple nature and the prompt desensitization effectiveness of administration discover. It is shown to above-mentioned Journal of Pharmaceuticsand Pharamcology Vol.41 803-805 1989 by by medicating healthy people with the pernasal liquids and solutions of buprenorphine that the effective blood drug concentration of a drug was accepted promptly. However, even if it makes it this pharmaceutical preparation, in order to make it the pharmaceutical preparation which can actually be equal to a patient's clinical use, it is important [ the physical stability of the chief remedy buprenorphine in pharmaceutical preparation is very a problem, and ] to conquer the problem of this stability.

## EFFECT OF THE INVENTION

[Effect of the Invention] Only injections or suppositories is conventionally marketed by this invention, but when a patient senses a pain for the buprenorphine which could not be prescribed for the patient only by the injection by the medical practitioner, or the rectum by the third person, the patient itself can prescribe a medicine now for the patient easily, desensitization can be performed promptly, and the effectiveness which this invention brings to a medical site can be called great thing.

## TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The purpose of this invention cancels a patient's pain promptly, and offering the pernasal powder pharmaceutical preparation of stable buprenorphine also physically has the administration simple.

## MEANS

[Means for Solving the Problem] That is, this inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and offer the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid.

[0008]

[Embodiment of the Invention] This inventions are buprenorphine and water poor solubility, are the basis of water absorptivity, and water absorptivity, and are the basis of a gel plasticity, and the pernasal pharmaceutical preparation of the shape of powder which consists of stearin acid.

[0009] The buprenorphine of this invention is the partialness agonist of morphine, and it is known that the analgesic action is dozens times the morphine. That is, when buprenorphine controls the nociception conduction system of a central nervous system, sad effectiveness is demonstrated and chemical stimulation, thermal stimulation, pressure stimulation, and electrical stimulation are made into a noxious stimulus, it is known that an analgesic effect strong and longer than morphine and pentazocine is shown. Kamiichi of injections and the suppositories is carried out as current and buprenorphine hydrochloride. The buprenorphine of this invention has also included the buprenorphine which exists as a salt with the acid permitted pharmacologically, and is buprenorphine hydrochloride which is a hydrochloride preferably.

[0010] The basis (it may abbreviate to a "water poorly soluble basis" below) of the water poor solubility of this invention and water absorptivity is one sort chosen from crystalline cellulose, alpha cellulose, a bridge formation dextran, a chitin, and the

group that consists of chitosan, or two sorts or more.
[0011] Also in these, as a water poorly soluble basis of this invention, one sort or two sorts or more of things chosen from the group which consists of crystalline cellulose, alpha cellulose, and chitosan are desirable, and can raise crystalline cellulose also especially with inside as a desirable thing.
[0012] It is the water absorptivity of this invention, and as for the basis (it may abbreviate to a "gel plasticity basis" below) of a gel plasticity, it is desirable that it is the low-grade alkyl of a cellulose, and it is desirable that they are one sort or two sorts or more of bases chosen from the group which consists of hydroxypropylcellulose, the hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose, and carboxymethylcellulose sodium especially. Hydroxypropylcellulose can be raised as a desirable thing even especially in inside.
[0013] Moreover, as for hydroxypropylcellulose, it is desirable that the viscosity of the 2% water solution is 150-4,000cps. Viscosity here is kinematic viscosity and it is measured by viscometers, such as an object for canon-Fenske and canon-Fenske opaque liquid, Ubbelohde, and Ostwald. Measurement by the ubellohde's viscosimeter has a highly desirable precision especially. The bottom of a 37-degree C environment is asked for a viscosity value given in this specification by the ubellohde's viscosimeter by the Shibata science mechanical-engineering company. Although there is also a thing of hypoviscosity in hydroxypropylcellulose from this, when the thing of hypoviscosity is used rather than 150cps, the rise effectiveness of the maximum drug concentration of this invention is not sometimes necessarily enough.
[0014] As a desirable combination of the gel plasticity basis of this invention, and a water poorly soluble basis, each above suitable example comrade's combination is mentioned, and the hydroxypropylcellulose as a gel plasticity basis and the crystalline cellulose as a water poorly soluble basis can be especially mentioned as a desirable combination.
[0015] The mixing ratio of the gel plasticity basis and water poorly soluble basis which are used by this invention is a weight ratio, since pernasal absorption of a drug with the higher and early direction with few 1:99-35:65, and gel plasticity bases is attained, it is desirable, and it is desirable that it is 10:90-20:80 especially.
[0016] Although, as for the stearin acid of this invention, the use on pharmaceutical preparation is originally known as lubricant, as for the operating concentration in that case, 0.3 - 1% has been common sense for this contractor. Wholeheartedly, although stearin acid committed this invention persons also as lubricant as a result of examination so that it might be well-known, it found out stabilizing pharmaceutical preparation by adding more mostly than the amount of general [ used ]. This is clearer than the stabilization effect of this invention was accepted [ that functionality is in the addition and stability of stearin acid (refer to example), and ] neither with the magnesium stearate which are other lubricant, nor talc (refer to the example of contrast). Therefore, since it is desirable that it is 0.1 - 10% and the addition and stability of stearin acid have correlation as mentioned above about the content of the stearin acid of this invention, that it is more 1 - 5% especially leads to stabilization further, and it is more desirable than 0.5% used as lubricant.
[0017] Moreover, in the pernasal pharmaceutical preparation of this invention, since that it is 150 micrometers or less improves [ the effectiveness after administration ] the particle diameter of a drug deposition into a nasal cavity, it is desirable, and since higher and early pernasal absorption of a drug is attained, it is desirable to set mean particle diameter to 1-100 micrometers and further 1-20 micrometers by grinding,

freeze drying, spray drying, etc. especially.

[0018] Moreover, in the pernasal pharmaceutical preparation of this invention, since higher and early pernasal absorption of a drug is attained, it is desirable that it is in the condition which a drug is unevenly distributed in a water poorly soluble basis, and is distributing rather than the gel plasticity basis. The following technique can be raised as the pharmaceutical preparation-technique of attaining this maldistribution.

1. Mix this water poorly soluble basis and a drug strongly mechanically. Subsequently, this gel plasticity basis is mechanically mixed weakly into this mixture.

2. Obtain the basis which the drug was made to adhere to this water poorly soluble basis by freeze drying or spray drying, and adhered the drug. Subsequently, it grinds and screening of the obtained basis is carried out so that the mean particle diameter of 90% of the weight or more of the particle may be set to 10-250 micrometers, and a powdered material is obtained. Then, this gel plasticity basis is mechanically mixed to this powdered material.

3. Dissolve and distribute this water poorly soluble basis and a drug in organic solvents, such as ethanol, and mix this gel plasticity basis mechanically to this powdered material after carrying out the particle size regulation of the fine particles obtained by evaporating and making that organic solvent harden by drying to the mean particle diameter of 10-250 micrometers.

[0019] Since it is easy among the above-mentioned manufacture approaches to consider as the condition that a drug is unevenly distributed in a water poorly soluble basis, and is distributing rather than the gel plasticity basis in the 1st manufacture approach and the 2nd manufacture approach, it is desirable. For example, in case it mixes strongly in case a water poorly soluble basis is mixed with a drug by the 1st manufacture approach, and it subsequently mixes with a gel plasticity basis, it can mix weakly. In case the gel plasticity basis of the 2nd manufacture approach is mixed mechanically, it can mix strongly or weakly.

[0020] Here, manual forcing mixing by the others and the mortar which are a high speed mixer, a power full auto mixer, etc. which are the omnipotent mixer, the ribbon mixer, the automatic mortar, the ball mill, etc. and the other mixers whose mechanical mixing at the time of manufacturing the constituent of this invention is mixers of a container cover half, such as a V shaped rotary mixer which is a mixer of for example, a container rotation mold, a cross rotary mixer, and a duplex cone mold mixer, is also included.

[0021] Moreover, mixing by mixing by manual mixing according mixing strongly in the case of mixing to a mortar, the omnipotent mixer of a container cover half, a ribbon mixer, an automatic mortar, a ball mill, etc. and the high speed mixer, a powerful auto mixer, etc. is said, and homogeneity is mixed while a drug mainly adheres to a basis by this mixing. Moreover, mixing by the ball mill which does not use the V shaped rotary mixer of a container rotation mold, a cross rotary mixer, a duplex cone mold mixer, and a ball as mixing weakly is shown, and distributed mixing of the drug is mainly carried out independently of a basis at homogeneity.

[0022] Furthermore, the pernasal pharmaceutical preparation of this invention can be prepared also by specifying the particle diameter of a basis as follows besides the manufacturing method of the above 1-3, and since these invention objects can also attain early high pernasal absorption of a drug, they are desirable. As an approach of specifying the particle diameter of a basis, it is the range whose mean particle diameter of 90% of the weight or more of the particle of water poorly soluble ** this basis is 10 micrometers - 250 micrometers, and is the range whose mean particle diameter of the particle of 90 % of the weight or more of ** this gel plasticity bases is

10 micrometers - 105 micrometers, and the approach of preparing by making mean particle diameter of ** water poorly soluble basis larger than the mean particle diameter of this gel plasticity basis can be mentioned, for example.

[0023] Furthermore, when mean particle diameter of 90% of the weight or more of the particle of 10-250 micrometers and a gel plasticity basis is set to 10-65 micrometers for the mean particle diameter of 90% of the weight or more of the particle of a water poorly soluble basis, since the increment in the further maximum drug concentration can be acquired, it is desirable.

[0024] That it is in the range whose mean particle diameter of 90% of the weight or more of the particle of a basis is 10-250 micrometers here says what gave vibration with hand control or a machine, was specified by classifying powder, passed the sieve whose aperture of an eye is 250 micrometers using the trial sieve machine, and did not pass a 10-micrometer sieve. Under the present circumstances, while giving vibration, it is a time of carrying out weighing capacity of the weight of the fine particles on each sieve, making the time of fluctuation of that weight becoming 0.1% or less into the terminal point of vibration, and the classification of fine particles being completed.

[0025] Moreover, even when the mean particle diameter of both bases is that the mean particle diameter of a water poorly soluble basis is larger than the mean particle diameter of a gel plasticity basis in above-mentioned numeric-value within the limits, respectively, it says that the numeric value of the mean particle diameter of a water poorly soluble basis is larger than the numeric value of the mean particle diameter of a gel plasticity basis.

[0026] Thus, the powdered pernasal administration constituent of this invention at the time of being prepared when the mean particle diameter of a water poorly soluble basis makes it larger than the mean particle diameter of a gel plasticity basis can be prepared according to the manufacturing method of common powdered pharmaceutical preparation for the person of this contractor of mixing mechanically a chief remedy, a water poorly soluble basis, and a gel plasticity basis.

[0027] By preparing according to the further above-mentioned manufacturing method of 1-3, since higher effectiveness can be acquired, it is desirable.

[0028] In addition, as the water poorly soluble basis and gel plasticity basis of this invention, unless it is contrary to the purpose of this invention, it has said specific property, and consists of a basis of a specific class, for example, it is desirable well-known as a basis which can be used for powder constituents for pernasal administration, such as starch and crystalline cellulose, to be able to use a microsphere and to use the thing of the range of 10 to 150 micrometers as a particle size of the particle in that case.

[0029] Moreover, to the constituent of this invention, the physical properties as pharmaceutical preparation, an appearance, or in order to improve that it is stinking etc., a well-known binder and a well-known diluent, a coloring agent, a preservative, antiseptics, an odor-masking agent, etc. may be added if needed. As a binder, if starch, a dextrin, etc. consider [ starch, a lactose etc. ] as; coloring agent as a; diluent, for example, and red No. 2 etc. considers [ an ascorbic acid etc. / p-hydroxybenzoic esters etc. ] as; odor-masking agent as; antiseptics as a; preservative, for example, menthol etc. is mentioned, for example.

[0030] Moreover, since the constituent of this invention is prescribed for the patient as pharmaceutical preparation, it is made into a suitable administration gestalt. As such a gestalt, there is a capsule filled up with this invention for every administration unit, and this is sprayed into a nasal cavity with a suitable administration vessel. moreover,

the constituent of this invention of administration unit quantity or the constituent of this invention of the administration unit quantity for multiple times -- a suitable container -- containing -- the time of administration actuation -- the constituent of this invention of administration unit quantity -- single-dose administration -- or division administration may be carried out.

EXAMPLE

[Example] An example explains this invention below.

[0033] [Examples 1-5] The pernasal pharmaceutical preparation which used buprenorphine as the chief remedy by the formula shown in the 1st following table was prepared.

[0034] [Table 1]

単位＝mg

| 実施例 | ブプレノルフィン | 結晶性セルロース | ヒドロキシプロピルセルロース | ステアリン酸 |
|---|---|---|---|---|
| 実施例1 | 40 | 1600 | 400 | 2 |
| 実施例2 | 40 | 1600 | 400 | 10 |
| 実施例3 | 40 | 1600 | 400 | 20 |
| 実施例4 | 40 | 1600 | 400 | 100 |
| 実施例5 | 40 | 1600 | 400 | 200 |

[0035] [Examples 1-3 of contrast] The pernasal pharmaceutical preparation which used buprenorphine as the chief remedy by the formula shown in the 2nd following table was prepared.

[0036] [Table 2]

単位＝mg

| 対照例 | ブプレノルフィン | 結晶性セルロース | ヒドロキシプロピルセルロース | 滑沢剤 |
|---|---|---|---|---|
| 対照例1 | 40 | 1600 | 400 | ステアリン酸マグネシウム：10 |
| 対照例2 | 40 | 1600 | 400 | タルク：10 |
| 対照例3 | 40 | 1600 | 400 | なし |

[0037] The result of having measured 20mg of contents under preservation by 60 degrees C and 40-degree-C75%RH at a time for the buprenorphine pernasal pharmaceutical preparation prepared by the buprenorphine pernasal pharmaceutical preparation prepared according to examples 1-5 and the examples 1-3 of contrast for the glass vial, respectively was shown in the 3rd table.

[0038] [Table 3]
ブプレノルフィン経鼻製剤の含量[%]変化

| 製剤 | 初期値 | ６０℃保存４週間後 | ４０℃７５%RH保存６ヶ月後 |
|---|---|---|---|
| 実施例１ | １００ | ９５．５% | ９５．０% |
| 実施例２ | １００ | ９５．０% | ９６．０% |
| 実施例３ | １００ | ９７．０% | ９７．５% |
| 実施例４ | １００ | ９９．０% | ９９．０% |
| 実施例５ | １００ | ９８．５% | ９９．５% |
| 対照例１ | １００ | ７５．０% | ６４．０% |
| 対照例２ | １００ | ８０．５% | ７５．５% |
| 対照例３ | １００ | ８０．５% | ８０．０% |